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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,126	06/22/2001	Jennifer L. Schmitke	2685.2030-000	9053

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EXAMINER	
HAGHIGHATIAN, MINA	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 11/20/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,126	SCHMITKE ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al (5,985,309) in view of Patton et al (5,997,848).

Edwards teaches particle incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system, methods of preparation and administration. Exemplary surfactants include dipalmitoylphosphatidylcholine (DPPC). Exemplary hydrophilic or hydrophobic complexes include insulin and protamine. The particles are aerodynamically light particles with a tap density of less than 0.4 g/cm^3, a mean diameter between 5 and 30 micron and an aerodynamic diameter between 1 and 5 microns (col. 3, line 56 to col. 4, line 17).

Edwards discloses that administration of the particles to the lung by aerosolization permits deep lung delivery of relatively large diameter therapeutic aerosols, for example greater than 5 micron in mean diameter. The particles can be fabricated with features which enhance aerosolization via dry powder inhaler devices, and lead to lower deposition in the mouth, throat and inhaler device (col. 5, lines 29-47).

Edwards also discloses that in addition to the therapeutic agents, the formulations may and preferably do include one or more excipients such as **sugars**, proteins and surfactant (col. 6, line 65 to col. 7, line 2). Targeting molecules can be attached to the particles via reactive functional groups on the particles. For example, targeting molecules can be attached to the amino acid groups of functionalized polyester graft copolymer particles such as poly(lactic acid-co-lysine) (col. 11, lines 48-60). Therapeutic agents suitable for such preparation include **insulin** (col. 12, lines 16-47).

Edwards discloses examples of particles such as insulin:albumin:lactose:DPPC in example 9. The particles are said to comprise 60% DPPC, 2% insulin, 19% albumin and 19% lactose. Two solutions are made of the ingredients, then they are combined and spray dried to produce particles. Example 11 discloses preparation method of sustained release insulin particles and example 12 discloses preparation of insulin:protamin:zinc complexes. Edwrads lacks specific disclosure of sodium citrate in the preparations

Patton teaches that systemic delivery of insulin to a mammalian host is accomplished by inhalation of a dry powder of insulin, which is rapidly absorbed through the alveolar regions of the lung. Insulin dry powders are prepared by dissolving insulin in an aqueous buffer to form a solution and spray drying the solution to produce substantially amorphous particles having a particle size less than 10 micron, preferably less than in the range of 0.1 to 5 micron. Optionally the pharmaceutical carrier is also dissolved in the buffer, to form a homogenous solution, wherein spray drying of the

solution produces individual particles comprising insulin, carrier buffer and any other compounds which were present in the solution. The carrier is preferably an amino acid, such as glycine, lysine, etc (col. 3, lines 9-21; 53-68 and col. 4, lines 43-60).

Patton discloses that insulin dry powders suitable for use in the present invention include amorphous insulin, crystalline insulin or mixtures thereof. The preferred method of forming insulin powders comprising particulates in the desired size range is spray drying, where pure bulk insulin is first dissolved in a physiologically acceptable aqueous buffer, typically a citrate buffer such as sodium citrate (col. 6, lines 11-16 and 43-67). The preferable concentration ranges for insulin is 5 to 95% and for the carrier material is 5 to 95%. The presence of carrier material in the particles which are delivered to the alveolar region of the lung has been found not to significantly interfere with systemic absorption of insulin (col. 7, lines 1-27).

Patton also discloses that the individual dosages on a per inhalation basis, typically being in the range from 0.5 mg to 10 mg, and the total dosage during a single respiratory administration is in the range of 0.5 to 15 mg (col. 8, lines 25-32).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the formulations of Edwards containing insulin DPPC and excipients such as lactose with insulin formulations and method of delivering the insulin formulations to the lung as taught by Patton and to have substituted lactose with sodium citrate since Patton discloses that lactose and sodium citrate are equivalent

carriers. Furthermore, sodium citrate acts as both a carrier and a buffer and thus its dual function is a motivation for one of ordinary skill to select sodium citrate over lactose.

Double Patenting

Claims 1-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/ 179,463. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims of the copending application No. 10/179,463 are within the scope of the claims of the instant application. In particular, for example in claim 1, "60% DPPC" is within the range of "approximately 60% DPPC". Also in dependent claims the variation of concentration ranges for DPPC is an optimization of ranges and would vary according to the amount of active agent desired for the preparation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments with respect to claims 1-60 have been considered but are moot in view of the new ground(s) of rejection. However since two of the prior art references apply to the new rejection, arguments regarding the said references will be addressed.

Applicant argues that "Edwards may teach compositions possessing insulin and DPPC the exact ingredients and their proportions confer significant differences in terms of rate of release into the patient in need of treatment" (see page 11). This is not commensurate with the scope of the claims. The claims are drawn to "A formulation" and the Edwards reference clearly meets the required components of the formulation, not specifically disclosing sodium citrate. Patton et al is disclosing a formulation for inhalation containing insulin and a carrier. Patton teaches that the carrier can be selected from the group consisting of sugars such as lactose or sodium citrate (see col. 6, lines 43-60). Patton is clearly teaching that lactose and sodium citrate are equivalent and even goes as far as stating that the preferred group of carriers include sodium citrate. Edwards is teaching that a charged therapeutic agent such as insulin can be administered as a complex between the charged agent and a molecule of opposite charge such as charged lipid (see col. 12, lines 42-47).

Applicant, with regards to Patton reference, states that "with respect to the size ranges, the examiner states that the size ranges are less than 10 microns, preferably less than in the range of 0.1 to 5 microns. In reality the sizes of the powders in the examples were below 5 microns". The point of this argument is not clear since 1) a range of 0.5 to 5 micron includes a) a less than 5 microns range and b) a 1-3 microns range, 2) a preferred embodiment does not teach away form the broader disclosures. Applicant argues that with regards to delivery by inhalation of dry powder on insulin, the Patton's teaching is much narrower (see page 14 of Response). This is not correct. Patton is clearly disclosing delivery of insulin by inhalation. In fact the abstract reads

"Systemic delivery of **insulin** to a mammalian host is accomplished by **inhalation** of a **dry powder** of insulin". The summary of the invention reads "it ha been found that inhaled dry insulin powders are deposited in the alveolar regions of the lung and rapidly absorbed through the epithelial cells of the alveolar region into blood circulation. Thus pulmonary delivery of insulin powders can be an effective alternative to administration by subcutaneous injection". Applicant also argues that Patton discloses a two-step method of delivery for the insulin. This is not commensurate with the scope of the claims since the instant claims do not exclude a two-step method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 703-308-6330. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 703-308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

MICHAEL G. HARTLEY
PRIMARY EXAMINER

Mina Haghighatian
November 18, 2003